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## Diet-induced alteration in the activity of plasma lipid transfer protein in normolipidemic human subjects

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### Summary

Studies were performed to investigate the effect of diets rich in oleic or linoleic acids on the activity of plasma cholesteryl ester transfer protein (CETP) in normolipidemic subjects. Previous to the test diets, all subjects consumed a baseline diet rich in saturated fatty acids ("sat-diet") for 17 days. The test diets, rich in either monounsaturated fatty acids ("mono-diet") or rich in polyunsaturated fatty acids ("poly-diet"), were given for 5 weeks to 52 normolipidemic healthy volunteers. The activity of CETP was measured, using a method independent of endogenous plasma lipoproteins, as the rate of exchange of radioactive cholesteryl oleate between labelled LDL and unlabelled HDL. The "mono-diet" induced a statistically significant decrease in CETP activity (from  $115 \pm 20$  to  $102 \pm 19$  units/ml plasma,  $P < 0.01$ ), while the small decrease on the "poly-diet" (from  $111 \pm 23$  to  $107 \pm 22$  units/ml plasma) did not reach significance. The percentual decrease in CETP activity induced by the "mono-diet" was higher than that induced by the "poly-diet" as was also found for the decrease in LDL cholesterol. In both diet groups a positive correlation was found between changes in CETP activity and changes in plasma total or (VLDL + LDL) cholesterol. The results suggest that high levels of dietary monounsaturated fatty acids may result in decreased plasma CETP activity, as well as LDL cholesterol levels. The mechanisms of these effects, and their possible interrelations, remain to be established.

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**Key words:** Lipid transfer protein; Cholesteryl ester transfer protein; Man; Diet; Monounsaturated fatty acids; Polyunsaturated fatty acids; Lipoprotein

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### Introduction

Human plasma contains a lipid transfer protein (CETP) which catalyses the transfer of cholesteryl

esters (CE), triglycerides (TG) and phospholipids between lipoproteins [1–6]. This process of lipid transfer leads to major alterations in the composition of lipoproteins and therefore affects lipoprotein metabolism. Although the function of CETP has been partially identified, little is known about the regulation of CETP activity in human plasma. It has been reported that the activity of CETP is increased in hypercholesterolemic [7] and dysbetalipoproteinemic subjects [8]. In hyperlipidemic subjects fed a high-fat or low-fat diet the activity of CETP changed in parallel with the concentration of (VLDL + LDL) cholesterol [9]. Animal studies with rabbits, a species with a high CETP activity, showed that elevations in the activity of CETP go together with elevations in plasma total cholesterol and (VLDL + LDL) cholesterol, both in diet-induced hypercholesterolemia and in hypercholesterolemia caused by a genetic defect in the LDL receptor [10,11]. In hyper- and hypo-responding rabbits, diet-induced hypercholesterolemia coincides with increases in CETP activity [12]. A similar diet-induced effect on CETP has been reported in the hamster, although the plasma CETP activity in this species is much lower than in man and rabbit [13]. All these studies deal with hyperlipidemic situations.

In this report we focus on the effect of diets rich in monounsaturated fatty acids ("mono-diet") or rich in polyunsaturated fatty acids ("poly-diet") on the activity of plasma CETP. The activity of CETP was determined independent of the lipoproteins present in the plasma sample to be measured and was measured as exchange of CE between exogenous LDL and exogenous HDL. The measured activity is the result of the presence of CETP and the putative CETP-inhibitor [6,14,15].

It is the first report on diet-induced alteration in plasma CETP activity in normolipidemic subjects.

## Methods

### *Subjects and diet*

This study was approved by the Ethical Committee of the Department of Human Nutrition, Agricultural University, Wageningen. Detailed information on the characteristics of the subjects, the diets, and the study protocol is presented

elsewhere in a paper that describes the effects of the 2 diets on lipoprotein levels [16].

Fifty-two normolipidemic subjects, 22 men (age 20–48 years) and 30 women (age 19–45 years) volunteered in the study. The diets used differed only in the fatty acid composition. All subjects initially received a diet containing 19.3 energy % (en%) saturated fatty acids, 11.5 en% monounsaturated fatty acids, and 4.6 en% polyunsaturated fatty acids for 17 days (baseline period). After this period subjects received a diet rich in either mono-unsaturated fatty acids ("mono-diet": 12.9 en% saturated fatty acids, 15.1 en% monounsaturated fatty acids and 7.9 en% polyunsaturated fatty acids) or in polyunsaturated fatty acids ("poly-diet": 12.6 en% saturated fatty acids, 10.8 en% monounsaturated fatty acids and 12.7 en% polyunsaturated fatty acids) for 36 days (test period).

### *Sample collection*

Blood was collected after an overnight fast on day 14 and 17 (baseline period), and on day 50 and 53 (test period) in tubes containing EDTA (1.5 mg/ml) and placed on ice. Plasma was separated within 1 h and the plasma samples used for the measurement of CETP activity were frozen within 4 h. Samples were kept at  $-20^{\circ}\text{C}$  and analyzed within 5 months. All samples were analyzed separately and the means of the 2 samples of day 14 and 17 and of day 50 and 53 were used as the actual values. On the same days blood was sampled and serum was prepared for the measurement of serum lipids [16].

### *Measurement of CETP activity*

The activity of CETP in plasma was determined exactly as described by Groener et al. [17], using an isotope assay detecting the exchange of radioactive CE between [ $^{14}\text{C}$ ]cholesteryl oleate labelled LDL and unlabelled HDL. The measured activity, CETP activity, is independent of endogenous lipoproteins. Plasma samples were treated with polyethylene glycol to precipitate VLDL + LDL and the activity of CETP was measured in the (VLDL + LDL)-free plasma. In plasma of normal fasting subjects CETP is mostly present on HDL<sub>3</sub> and VHDL and very small amounts are found in the lipoprotein-free fraction [1,18,19].

Recently this localization of CETP in plasma was confirmed, using a radioimmuno assay for CETP [20]. The amount of HDL introduced with the (VLDL + LDL)-free supernatant to the assay system was less than 15% of the total amount of HDL present in the assay medium and does not affect the measurement. LDL and HDL, used for the measurement of CETP, were isolated from one batch of freshly isolated human plasma by repeated ultracentrifugation from densities  $1.006 < d < 1.063$  g/ml and  $1.063 < d < 1.21$  g/ml, respectively [21]. LDL was labelled with [ $^{14}$ C]cholesteryl oleate using the vesicle method described by Morton & Zilversmit [6]. All plasma samples were assayed in one week. Plasma samples from one subject were analyzed on one day. The within run variation was 2.7%. The differences in the CETP activity in the 2 samples from one subject taken at day 14 and 17 or at day 50 and 53 were  $6.3 \pm 4.9\%$ . This difference was calculated relative to the value on day 14 and day 50 respectively. Standard sera were used to control the day to day variation in the experiment. The day to day variation in this set of experiments was 7.7%. The activity of CETP can be calculated as nmoles cholesteryl esters exchanged/h/ml plasma [17]. Since the actual value of the CETP activity depends on the batches of labelled LDL and unlabelled HDL used, the activity of CETP is expressed in arbitrary units (units/ml plasma).

#### Other methods

Free cholesterol and total cholesterol in isolated lipoproteins were measured enzymatically

with kit nr. 310 328 (Boehringer Mannheim). Cholesteryl ester was calculated as the difference in total cholesterol and free cholesterol.

#### Data analysis

Statistical analyses are based on the entire sample of each diet group. Descriptive statistics, mean and standard deviation, are given separately for men and women. The paired Student *t*-test was used to determine significant differences between test and control samples. Student's *t*-test was used to analyze differences in changes due to the 2 test diets. Pearson correlation coefficients were used to measure the association between alterations in CETP and alterations in other lipid parameters. Relationships between CETP activity and lipid parameters, Quetelet index and age were estimated using Pearson correlation coefficient (*r*) and Spearman correlation coefficient (*r<sub>s</sub>*), as appropriate.

#### Results

CETP activity was normally distributed (both in men and women) while on the baseline high-saturated fat diet. It ranged from 68.1 to 154.9 units/ml plasma, with a mean of  $113 \pm 22$  units/ml. No difference was found between CETP activities in men and women.

Table 1 presents the CETP activity in plasma of all subjects at the end of the baseline and at the end of the test period. Subjects were divided into men and women, but statistical analyses were also

TABLE 1  
EFFECT OF "MONO-DIET" AND "POLY-DIET" ON CETP ACTIVITY (UNITS/ml PLASMA)

	Men		Women		All	
	"mono-diet"	"poly-diet"	"mono-diet"	"poly-diet"	"mono-diet"	"poly-diet"
Baseline	114 $\pm$ 17	117 $\pm$ 19	116 $\pm$ 24	107 $\pm$ 26	115 $\pm$ 20	111 $\pm$ 23
Test	99 $\pm$ 16 *	111 $\pm$ 15	104 $\pm$ 21 *	104 $\pm$ 26	102 $\pm$ 19 **	107 $\pm$ 22
Percent change					- 10.2 $\pm$ 10.4	- 3.1 $\pm$ 11.9
95% confidence level						- 14.3 to - 1.8 +

Values are mean  $\pm$  S.D. Significant differences between the values in the baseline period and the test period by paired Student *t*-test: \* *P* < 0.01; \*\* *P* < 0.001. + denotes a significant difference in changes between diet groups (*P* < 0.05). Baseline values were measured after 14 and 17 days on a baseline diet rich in saturated fatty acids ("sat-diet"). Test values were measured on day 50 and 53 of the experiment, i.e. after 33 and 36 days on diets either rich in monounsaturated fatty acids ("mono-diet") or rich in polyunsaturated fatty acids ("poly-diet").

performed on the whole diet group. No difference in CETP activity was found between the baseline samples of the 2 diet groups or between men and women. The data show a significant decrease in CETP activity in the "mono-diet" group, in both men and women. The small decrease in CETP activity in the "poly-diet" group was not statistically significant. It cannot be excluded completely that these decreases in CETP activity are simply caused by the time period between the baseline and test samples. Therefore the effects of the 2 diets were compared directly. CETP activity falls by  $10.2 \pm 10.4\%$  on the "mono-diet" and by  $3.1 \pm 11.9\%$  on the "poly-diet" (95% confidence interval of the difference in percentual change between the 2 diets groups:  $-14.3\%$  to  $-1.8\%$ ).

Table 2 shows a summary of the measured lipid parameters, in so far as they are of importance for the interpretation of the present data. More detailed information on the effects of the diets on the different lipoprotein parameters has been presented elsewhere [16].

Responses of CETP activity and lipid levels to the two different diets were compared and Pearson correlation coefficients were calculated. In both diet groups changes in CETP activity correlated positively with changes in (VLDL + LDL) cholesterol ("mono-diet":  $r = 0.471$ ,  $P = 0.02$ ; "poly-diet":  $r = 0.509$ ,  $P = 0.01$ ), total cholesterol ("mono-diet":  $r = 0.366$ ,  $P = 0.07$ ; "poly-diet":  $r = 0.525$ ,  $P = 0.01$ ), LDL-cholesterol ("mono-diet":  $r = 0.390$ ,  $P = 0.05$ ; "poly-diet":  $r = 0.508$ ,  $P = 0.01$ ), but not with HDL-cholesterol. Analyzing alterations in CETP activity and alterations in plasma lipid values introduced by the 2 diets together revealed significant positive correlations between changes in CETP activity and changes in

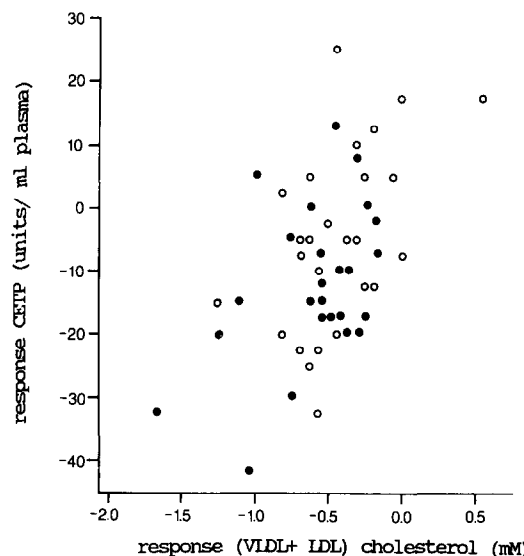


Fig. 1. Relationship between CETP-response and (VLDL + LDL) response in the "mono-diet" group ( $r = 0.471$ ,  $P = 0.02$ ) and the "poly-diet" group ( $r = 0.509$ ,  $P = 0.01$ ). Response is defined as the difference between the test period and the baseline period. Pearson correlation coefficient ( $r$ ) for all subjects is 0.523 ( $P = 0.0001$ ). ●, "mono-diet"; ○, "poly-diet".

(VLDL + LDL) cholesterol ( $r = 0.523$ ,  $P = 0.0001$ ), total cholesterol ( $r = 0.492$ ,  $P = 0.0002$ ) and LDL-cholesterol ( $r = 0.497$ ,  $P = 0.0002$ ), but not with changes in HDL-cholesterol. Fig. 1 presents the data for the relationship between changes in CETP activity and changes in (VLDL + LDL) cholesterol.

The baseline samples obtained in this study reflect the CETP activity and lipoprotein levels on a "Western" type diet and were used to determine the relationship between CETP activity and age, Quetelet index and lipoprotein levels. Positive correlations were found between CETP activity and (VLDL + LDL) cholesterol ( $r = 0.285$ ,  $P = 0.04$ )

TABLE 2

EFFECTS OF THE "MONO-DIET" AND "POLY-DIET" ON SERUM LIPID LEVELS (IN mM)

Diet	Baseline			Test		
	Total chol.	HDL-chol.	TG	Total chol.	HDL-chol.	TG
"Mono-diet" group ( $n = 25$ )	$5.19 \pm 0.93$	$1.35 \pm 0.31$	$1.01 \pm 0.46$	$4.54 \pm 0.89$ *	$1.30 \pm 0.32$	$0.98 \pm 0.44$
"Poly-diet" group ( $n = 27$ )	$5.09 \pm 0.71$	$1.41 \pm 0.34$	$0.87 \pm 0.34$	$4.65 \pm 0.72$ *	$1.39 \pm 0.38$	$0.82 \pm 0.39$

Values are mean  $\pm$  S.D. Baseline values refer to the baseline diet ("sat-diet"), test values refer to the "mono-diet" or "poly-diet". Significant differences by paired Student's  $t$ -test: \*  $P < 0.001$ . For further information see legend of Table 1.

and LDL cholesterol ( $r = 0.289$ ,  $P = 0.04$ ) and negative correlation was found between CETP activity and HDL-cholesterol ( $r = -0.304$ ,  $P = 0.03$ ). No significant correlations ( $r_s$ ) were found between CETP activity and age or Quetelet index.

## Discussion

This study reports a decrease in the activity of CETP in normolipidemic subjects, consuming a diet enriched in monounsaturated fatty acids. The consumption of a diet enriched in polyunsaturated fatty acids resulted in a smaller (not significant) decrease. In both diet groups positive correlations were found between changes in CETP activity and changes in (VLDL + LDL) cholesterol, LDL cholesterol and total cholesterol. The results suggest that high levels of dietary monounsaturated fatty acids may specifically result in relatively low plasma CETP levels. The mechanism of this putative regulatory effect remains to be established. Alterations in the activity of CETP have been reported before in a diet study with hyperlipidemic subjects [9], where the changes in CETP activity coincided with changes in (VLDL + LDL) cholesterol. Animal studies have shown an increase in CETP activity parallel to an increase in plasma cholesterol under various conditions [10,11,13]. The latter studies deal with pronounced changes in the level of plasma cholesterol. The interesting feature of the present study is that natural mixed solid diets differing in unsaturated fatty acids, but not in saturated fatty acids or total fat, were used. It is interesting that the decrease in CETP activity on the "mono-diet", relative to the "poly-diet", parallels the decrease in plasma total, (VLDL + LDL), and LDL cholesterol. A high activity of CETP has been reported in hypercholesterolemic, dysbetalipoproteinemic and diabetic subjects [7,8,22], suggesting that high CETP activity coincides with high plasma (VLDL + LDL) cholesterol. At present it is impossible to assess whether the correlation of changes in CETP activity with changes in (VLDL + LDL) cholesterol points to a causal relationship. Since various situations of hypercholesterolemia all coincide with an increase in CETP activity, it may be that CETP activity is regulated by the level of (VLDL + LDL) cholesterol. This phenomenon has been thor-

oughly discussed for rabbits [10,11], but no underlying mechanism could be given. Recently Quintet et al. [23] reported that in cholesterol-fed rabbits the increased activity of CETP coincides with increased mass of CETP in plasma and increased mRNA levels in the liver, suggesting that increased hepatic synthesis of CETP is involved in this diet-induced change in plasma CETP in the rabbit. In rabbit CETP mRNA is only found in the liver, in contrast to the wide spread tissue distribution of CETP mRNA in man [23-25]. Human HepG2 cells, human monocyte-derived macrophages, and CaCo-2 cells derived from human enterocyte epithelium all synthesize and secrete CETP [26-29]. The secretion of CETP by the macrophages and the CaCo-2 cells is regulated. Cholesterol loading of the macrophages results in an increase in the secretion of CETP activity. This suggests that the secretion of CETP by macrophages may be under the influence of plasma (VLDL + LDL) cholesterol levels. Additional experiments are needed to clarify the regulation of CETP synthesis in man.

The baseline samples obtained in this study were used to determine possible relationships between plasma levels of CETP activity and certain population and lipoprotein parameters. In agreement with an earlier study [7] there were positive correlations between CETP activity and (VLDL + LDL) cholesterol, as well as with plasma total cholesterol, and a negative correlation with HDL cholesterol. Significant correlations between CETP activity and age or Quetelet Index on CETP activity were not observed.

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